REVIEW ARTICLE

Am J Cardiovasc Drugs 2010; 10 (3): 143-154
1175-3277/10/0003-0143/$49.95/0

Use of Calcium Channel Blockers in Cardiovascular Risk Reduction

Issues in Latin America

Luis Alcocer,[1] *Mario Bendersky,*[2] *Julio Acosta*[3] and *Miguel Urina-Triana*[4]

1 Universidad Nacional Autónoma de México, Hospital General de México, México City, México
2 Universidad de Córdoba, Córdoba University, Instituto Modelo Cardiología and Clinical Investigation Unit Rusculleda Foundation/DAMIC, Córdoba, Argentina
3 Policlínica Metropolitana, Caracas, Venezuela
4 Fundación Bios, Barranquilla, Colombia

Contents

Abstract

Cardiovascular disease (CVD) is a continuum that begins with the presence of several risk factors for CVD, including smoking, hypertension, obesity, diabetes mellitus, and high levels of cholesterol, and if unaddressed can result in premature death, ischemic heart disease, stroke, congestive heart failure, and end-stage renal disease. Hypertension is associated with a significant increase in cardiovascular (CV) morbidity and mortality, raising the risk of stroke, myocardial infarction, heart failure, kidney disease, and peripheral arterial disease. In Latin America, the prevalence of hypertension and other CV risk factors has become similar to that seen in more developed countries, increasing the proportion of the population at high risk for CVD and congestive heart failure; however, it is hypertension that is a key driving force behind CV risk in Latin America. Despite the existence of a wide range of antihypertensive agents, BP control and reductions in CV risk remain poor in Latin America and in Hispanics living in the US. Ethnic differences in treatment rates and disease awareness have been well documented. Studies have shown that calcium channel blockers (CCBs; calcium channel antagonists) are at least as effective in reducing BP and improving the CV risk profile as other classes of antihypertensive agents when administered as monotherapy. CCBs have also been shown to be effective when administered as part of combination therapy in both low- and high-risk hypertensive patients, suggesting that CCBs can easily be combined with other antihypertensive classes in order to achieve BP control and CV risk reduction. In patients with hypertension, coronary artery disease, and high cholesterol, CCBs have been associated with beneficial effects on a range of other aspects of the CV continuum, including the vasculature, coronary calcification, and progression of atherosclerosis. CCBs have also been shown to preserve renal function. Unlike diuretics and β-adrenoreceptor antagonists, CCBs are

metabolically neutral, inducing minimal changes in serum lipids and decreasing the incidence of new-onset diabetes compared with other antihypertensive agents. CCBs are well tolerated when administered as monotherapy or combination therapy, with long-acting formulations minimizing adverse events even further compared with short-acting formulations. These characteristics make CCBs an attractive option for the treatment of hypertension and CV risk in Latin America, which remain significant health issues in this region.

1. Update on Cardiovascular (CV) Risk in Latin America and the Importance of Hypertension

The pathophysiology of cardiovascular disease (CVD) has been described as a cardiovascular (CV) continuum that begins with the presence of risk factors for CVD, ultimately resulting in premature death, ischemic heart disease, stroke, and the development of congestive heart failure and end-stage renal disease.[1] The concept of a continuum has expanded into what is now recognized as a cardio-renal continuum, in which kidney damage increases CV risk, and vice versa, in a vicious circle. We now know that the development of CV and renal damage originates in a shared set of risk factors.

The management of patients at risk for CVD includes lifestyle changes with or without pharmacotherapy, and risk stratification at an early stage is highly important for guiding therapeutic decisions.[2] Data suggest that psychosocial stress is among the most important risk factors for CVD in Latin America, along with a history of hypertension;[3] additional risk factors include a history of diabetes mellitus, current smoking, increased waist : hip ratio, hypercholesterolemia, and high alcohol intake.[3-6]

Hypertension, defined as an SBP of ≥140 mmHg and a DBP of ≥90 mmHg,[2,7] is associated with a significant increase in CV morbidity and mortality. Hypertension increases the risk of stroke, myocardial infarction (MI), heart failure, kidney disease, and peripheral arterial disease.[2,8,9] For patients aged 40–70 years, the risk of hypertension-related adverse events doubles with every increase of 20 mmHg in SBP or 10 mmHg in DBP within the BP range of 115/75 to 185/115 mmHg.[10] Thus, the importance of BP control (defined as a BP <140/90 mmHg for hypertensive patients and <130/80 mmHg for diabetic hypertensive patients[2,11]) in reducing the incidence of adverse CV events cannot be underestimated.

A small proportion of patients with stage I hypertension (defined as an SBP or DBP of 140–159 and 90–99 mmHg, respectively[2]) may achieve good BP control with antihypertensive monotherapy, but most patients require two or more agents to achieve BP goals.[2] Despite the fact that a wide range of antihypertensive agents exists, control of BP and reductions in CV risk remain unacceptably poor. In the US during 2005 and 2006, only 64% of hypertensive patients achieved BP control, despite the use of antihypertensive medication.[12] While there were no ethnic disparities reported with respect to BP control rates, differences were seen in other areas; for example, Mexican Americans were less likely to be aware of their hypertension than non-Hispanic Blacks and were less likely to be receiving antihypertensive medication compared with non-Hispanic Whites and non-Hispanic Blacks.[12]

Calcium channel blockers (CCBs; calcium channel antagonists) are attractive therapeutic options in the treatment of hypertension, with increasing evidence that supports their use not only in patients with hypertension but also in normotensive patients with coronary artery disease (CAD). In this paper, we review the existing evidence for CCBs in the management of CV risk reduction, with a particular focus on the scope of the challenges in Latin America.

2. The Reality of CV Risk in Latin America

CVD is one of the leading causes of mortality in Latin America,[13] being responsible for around 800 000 deaths per year (around 25% of all deaths).[14] The death rate from ischemic heart disease and stroke in this region is also increasing; it is expected to triple between 1990 and 2020.[13] Latin America has been said to be in the initial phase of a CAD epidemic (reviewed by Cubillos-Garzon et al.[15]). The average age of the Latin American population is increasing, and with that comes increases in the prevalence of hypertension, obesity, diabetes, and metabolic syndrome – key risk factors in the development of CVD.[15-18] The prevalence of these risk factors in Latin America has become similar to that seen in more developed countries. For example, the prevalence of hypertension in Latin America in the late 1980s and 1990s averaged 20–23%, while the prevalence in the US during a similar period was 24%.[19,20] Similarities in prevalence between Latin America and the US are also seen with obesity and diabetes (reviewed by Cubillos-Garzon et al.[15]).

Estimated total deaths in 23 selected developing countries are expected to rise in 2015 and almost half of these deaths will occur in people younger than 70 years compared with only 27% in high-income countries.[21] This figure will rise to 53% in 2030 with an overall share of burden of disease in disability-adjusted life-years of almost 60%. Additionally, the long-term economic savings, by comparing gross domestic product levels under a scenario of achieving a 2% yearly additional reduction in mortality rates from chronic diseases, as recommended by the WHO, would save almost 10% of the expected loss in income in these countries.[22]

Hypertension is a key driving force for CV risk in Latin America. However, the incidence of hypertension and other CV risk factors varies widely across the region, probably due to a number of factors, such as differences in the incidences of smoking and obesity, and ethnic variation. Moreover, epidemiological studies in Latin America have been impeded by methodological inconsistencies, such as risk-factor definitions, variations in the age of individuals enrolled, poor sampling techniques, and methods of assessment.[23] A recent population-based study of individuals aged 25–64 years in seven Latin American cities reported a prevalence of hypertension that ranged from 24–29% in Santiago (Chile), Barquisimeto (Venezuela), and Buenos Aires (Argentina), to as low as 9% in Quito (Ecuador).[24] Another study reported a prevalence of hypertension of 30% among 15- to 85-year-olds in Cordoba (Argentina).[25] Diagnosis and management of hypertension in Latin America generally follows the guidelines of the Joint National Committee,[2] the WHO/International Society of Hypertension (ISH),[11] and the ISH/European Society of Cardiology (ESC).[26]

Approximately 80% of the burden of BP-attributable diseases occurs in low- and middle-income countries (Latin America included), with BP-attributable death rates 1.5- to 2-fold higher in low- or middle-income regions compared with high-income regions. A greater proportion of this disease burden occurs in younger people. About half of this burden is in people with an SBP <145 mmHg.[21] Many countries, such as Argentina, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela, have developed their own guidelines. A Latin American consensus in hypertension and a Latin American consensus in diabetes and hypertension have been published.[27-29]

Ongoing issues in antihypertensive therapy in Latin America are the same as those observed elsewhere. For example, BP control rates are unacceptably low, with rates as low as 13% and 15% reported in Argentina and Cuba.[25,30] Inadequate financial investment in healthcare represents an additional barrier to successful management of hypertension in Latin America. For example, while 11.6% of the worldwide burden of death and disability from all causes is attributed to developed countries, these countries account for over 90% of healthcare expenditure.[31] Hypertension must compete with other chronic diseases that have less of an overall impact on morbidity and mortality for a share of healthcare expenditure, and this may result in a disproportionate distribution of funds with respect to health outcomes. Indeed, data from Mexico indicate that only 6–8% of the total health budget is allocated to hypertension.[32] These dismal observations warrant a call to action for improved control of high BP and other CV risk factors across Latin America. Achieving these ambitious goals will require collaborative efforts by many groups, including policy-makers, international organizations, healthcare providers, schools, and society as a whole.[33]

3. Calcium Channel Blocker (CCB) Monotherapy: BP Control and Associated CV Risk Reduction

When administered as monotherapy, CCBs have generally been shown to be at least as effective, if not more effective, compared with other hypertensive classes in terms of BP control in patients with hypertension. In a crossover study of previously untreated hypertensive patients, CCBs were as effective at reducing SBP as diuretics and significantly ($p < 0.005$) more effective than ACE inhibitors and β-adrenoreceptor antagonists (β-blockers).[34] In high-risk patients with hypertension, amlodipine therapy resulted in significantly greater BP reductions than valsartan therapy (17.3/9.9 mmHg vs 15.2/8.2 mmHg; $p < 0.0001$) and a greater number of patients achieving BP control (62% vs 56%) in the VALUE study[35] (see table I for trial names). Nifedipine monotherapy has also demonstrated good efficacy in hypertensive patients who have at least one additional risk factor; in INSIGHT, a long-acting gastrointestinal transport system (GITS) formulation of nifedipine was as effective as co-amilozide (hydrochlorothiazide [HCTZ] plus amiloride) with respect to reduction in SBP, DBP, and the proportion of patients achieving BP goal (≥50% in both treatment groups).[36]

BP reductions were generally similar to those seen with other agents in patients receiving diltiazem in the NORDIL study[37] or verapamil in the CONVINCE trial.[38] Effective lowering of SBP and DBP was seen in both groups in the NORDIL study; BP reductions were 20.3/18.7 mmHg in the diltiazem group and 23.3/18.7 mmHg in the diuretic and β-blocker group.[37] In the CONVINCE trial, 65.5% of verapamil recipients and 65.9% of patients receiving atenolol or HCTZ achieved a BP target of

Table I. Trial names

Acronym	Name
ACCOMPLISH	Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension
ACTION	A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system
ADVANCE-Combi	Adalat CR and Valsartan Cost-Effectiveness Combination
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
BENEDICT	Bergamo Nephrologic Diabetes Complications Trial
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
COACH	Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure
CONVINCE	Controlled Onset of Verapamil Investigation of Cardiovascular Endpoints
ENCORE	Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function
FACET	Fosinopril vs Amlodipine Cardiovascular Events Randomized Trial
INSIGHT	International Nifedipine GastroIntestinal Transport System Study: Intervention as a Goal in Hypertension Treatment
INVEST	International Verapamil-Trandolapril Study
J-MIND	Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetes
M-FACT	Metoprolol Succinate-Felodipine Antihypertension Combination Trial
MARVAL	Microalbuminuria Reduction With Valsartan;
MIDAS	Multicenter Isradipine Diuretic Atherosclerosis Study
NICE-Combi	Nifedipine and Candesartan Combination
NORDIL	Nordic Diltiazem
REACH	Reduction of Atherothrombosis for Continued Health
TALENT	STudy EvALuating the Efficacy of Nifedipine GITS – Telmisartan Combination in Blood Pressure Control
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VHAS	Verapamil in Hypertension and Atherosclerosis Study

<140/90 mmHg.[38] The efficacy of CCBs in lowering BP has also been demonstrated in a number of other large studies in which patients with hypertension were treated with nicardipine,[39] felodipine,[40] or nitrendipine.[41]

CV risk has been associated more strongly with SBP than with DBP.[42] Indeed, it is estimated that around half of all disease burden occurs in individuals with an SBP of 130–150 mmHg.[43] The finding that nifedipine effectively reduces SBP is, therefore, highly important. Of note, in addition to its effectiveness in patients with essential hypertension, nifedipine was shown to be effective at reducing SBP in patients with isolated systolic hypertension in a subanalysis of patients from the INSIGHT trial.[44] Use of CCBs is therefore associated with a reduction in CV risk in a wide range of hypertensive patients.

CCBs are associated with substantial improvements in the CV risk profile. Compared with placebo, CCBs have been shown to significantly reduce the incidence of CV events in patients with hypertension.[41,45] When CCBs are compared with other antihypertensive classes, the effect on CV outcomes is generally similar. The reduction in the incidence of stroke and MI was similar between amlodipine monotherapy and both valsartan and chlorthalidone monotherapy in two studies.[35,46] In the ALLHAT trial, 11.3% and 11.5% of patients with hypertension and at least one CV risk factor receiving amlodipine and chlorthalidone, respectively, experienced the primary combined endpoint of fatal CAD or nonfatal MI.[46] The VALUE study had a combined primary endpoint of cardiac mortality and morbidity, which occurred in 10.4% and 10.6% of patients receiving amlodipine and valsartan, respectively.[35]

In the INSIGHT study, nifedipine GITS monotherapy was as effective as co-amilozide for reducing the incidence of the primary composite endpoint of CV death, MI, heart failure, or nonfatal stroke; 6.3% and 5.8% of nifedipine and co-amilozide recipients, respectively, experienced these outcomes, and these rates corresponded to 18.2 and 16.5 primary endpoints per 1000 patient-years ($p = 0.34$).[36] Since the baseline data for the Framingham risk equation predicts an event rate of 34.5 primary endpoints per 1000 patient-years, treatment with nifedipine and co-amilozide reduced the number of CV events by approximately half of the expected rate.[36] A subanalysis of hypertensive diabetic patients enrolled in the INSIGHT study showed that while there was no difference in the primary endpoint between treatment groups, significantly fewer hypertensive diabetic patients receiving nifedipine than those receiving co-amilozide experienced the secondary composite endpoint of all-cause mortality, death from a vascular cause, and death from a nonvascular cause (14.2% vs 18.7%; $p = 0.03$).[47]

In the NORDIL study, no significant between-group differences in the rate of fatal and nonfatal stroke, MI, and other CV death occurred in patients receiving either diltiazem or a diuretic plus a β-blocker (16.6 vs 16.2 events per 1000 patient-years; relative risk [RR] 1.00; 95% confidence interval [CI] 0.87, 1.15).[37] Similarly, patients taking verapamil or atenolol or

HCTZ experienced a similar rate of stroke, MI, or CVD-related death in the CONVINCE study (hazard ratio [HR] 1.02; 95% CI 0.88, 1.18).[38]

4. CCBs in Combination Therapy: BP Control

As mentioned above, evidence from previous studies suggests that many patients require combination therapy in order to achieve BP goals, particularly those at high CV risk.[2] The optimal combination of antihypertensive agents, however, remains to be established. CCBs have been shown to effectively reduce BP when administered as part of combination therapy for hypertension in both low- and high-risk patients. In the ASCOT-BPLA study, the combination of amlodipine and the ACE inhibitor perindopril was associated with a similar reduction in both SBP and DBP as the combination of atenolol and a thiazide in high-risk patients (27.5/17.7 mmHg vs 25.7/15.6 mmHg).[48] In the ACCOMPLISH study, high-risk patients received amlodipine plus benazepril or benazepril plus HCTZ. Compared with benazepril plus HCTZ, BP control rates were higher and SBP reductions were greater with amlodipine plus benazepril.[49]

Adding an angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) to nifedipine was shown to yield additional BP control to that provided by either agent alone in patients with mild-to-moderate hypertension.[50] Importantly, the reduction in SBP was greater with the combination of nifedipine and losartan than with either agent alone. After 8 weeks of therapy, BP reduction was 23.3/15.3 mmHg in the combination group, and 16.3/11.4 mmHg and 18.9/12.5 mmHg in the losartan and nifedipine groups, respectively (losartan plus nifedipine vs losartan; $p < 0.05$).[50]

Adding an ARB to amlodipine has also been shown to enable greater BP reductions and increased BP control compared with either agent alone.[51,52] In the COACH study a combination of amlodipine and olmesartan medoxomil produced a BP reduction of 30.1/19.0 mmHg compared with 19.7/12.7 mmHg and 16.1/10.2 mmHg with amlodipine and olmesartan monotherapy, respectively.[51] In a separate study, a combination of amlodipine and valsartan produced BP reductions from baseline of 28.4/18.6 mmHg compared with 24.1/15.6 mmHg and 19.8/13.3 mmHg with amlodipine and valsartan monotherapy, respectively.[52]

In the NICE-Combi study, Japanese patients with essential hypertension whose BP remained uncontrolled after an 8-week course of candesartan monotherapy received either nifedipine controlled release plus candesartan combination therapy, or an increased dose of candesartan. As expected, more patients achieved BP goal with combination therapy than with up-titrated candesartan, and reductions in both SBP and DBP were significantly greater ($p < 0.0001$) [figure 1].[53] When CCBs were compared in another group of Japanese patients with essential hypertension in the ADVANCE-Combi study, nifedipine controlled release plus valsartan demonstrated significantly superior reductions in both DBP and SBP than amlodipine plus valsartan after 16 weeks (34.0/20.1 mmHg vs 27.0/15.9 mmHg; $p < 0.05$). The proportion of patients achieving BP goal was also significantly higher with nifedipine plus valsartan compared with amlodipine plus valsartan (61.2% vs 34.6%; $p < 0.001$).[54]

CCBs are effective and well tolerated when combined with β-blockers for the treatment of hypertension. In M-FACT, patients with uncomplicated hypertension were randomized to receive one of 16 treatment regimens comprising extended-release felodipine or metoprolol succinate monotherapy or a combination of the two agents.[55] BP reductions were similar with low-dose combination therapy and monotherapy, and combination treatment was better tolerated.

Verapamil-based treatment was as effective as atenolol-based therapy at lowering BP in patients with hypertension and CAD in INVEST.[56] In this trial, patients were randomized to receive either sustained-release verapamil or atenolol, and trandolapril and/or HCTZ was added to achieve BP goals. Joint National Committee on Prevention, Detection, Evaluation,

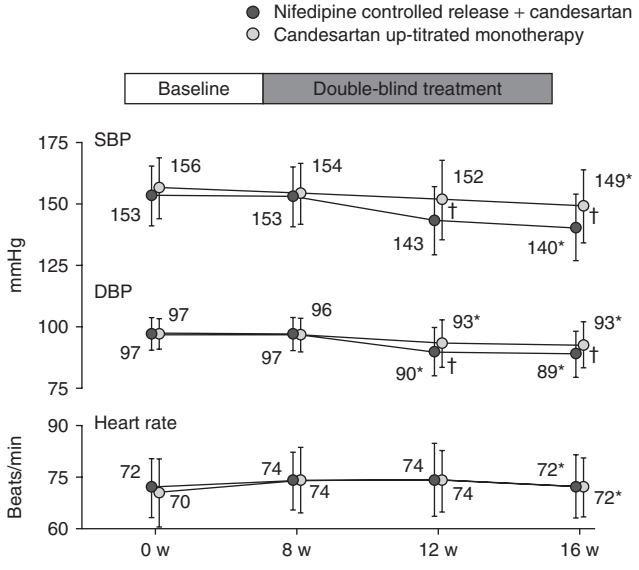

Fig. 1. Changes in SBP and DBP with nifedipine controlled release + candesartan or candesartan up-titrated monotherapy during 16 weeks of treatment (reproduced with permission from Hasebe and Kikuchi[53]). * $p < 0.05$ vs baseline; † $p < 0.05$ between treatment groups.

and Treatment of High Blood Pressure (JNC VI) goals for SBP and DBP were achieved in 65.0% and 88.5% of CCB recipients and 64.0% and 88.1% of patients receiving atenolol-based therapy.

There is also evidence that CCBs effectively reduce BP compared with placebo in patients receiving medication to treat CAD. The CAMELOT study evaluated patients with CAD and normal BP (<140/90 mmHg) who received placebo, amlodipine, or enalapril in addition to their existing medications, the most frequent (taken by >70% of patients) being β-blockers, statins, and aspirin (acetylsalicylic acid).[57] After 24 months of treatment, recipients of amlodipine and enalapril had reductions in BP (4.8/2.5 mmHg and 4.9/2.4 mmHg, respectively; $p < 0.001$ vs placebo), while placebo recipients had an increase in BP (0.7/0.6 mmHg).[57] In the ACTION study, patients with stable angina received either nifedipine GITS or placebo on top of best practice CV therapy (β-blockers and/or organic nitrate, administered either as needed or as daily maintenance therapy).[58] Control of both SBP and DBP was significantly greater with nifedipine than with placebo in this study. At baseline, 52% of patients had a BP ≥140/90 mmHg; at study end, 65% of patients who received nifedipine plus best practice CV therapy were controlled, compared with 53% of patients who received placebo plus best practice CV therapy.[58]

The ongoing TALENT study is investigating the efficacy of combining nifedipine GITS with telmisartan, an ARB with a long half-life, in approximately 400 patients at high CV risk because of the presence of diabetes, subclinical damage, or a metabolic syndrome.[59]

5. CCBs in Combination Therapy: CV Risk Reduction

The combination of amlodipine and perindopril was associated with a nonsignificant 10% decrease in the incidence of nonfatal MI and fatal CAD compared with the combination of atenolol plus a thiazide in the ASCOT-BPLA study.[48] However, compared with patients receiving atenolol/thiazide therapy, amlodipine/perindopril recipients experienced a decreased incidence of all-cause mortality (11% reduction; $p = 0.025$) and fatal and nonfatal stroke (23% reduction; $p = 0.0003$).[48] In the ACCOMPLISH study, the time to first CV morbidity or mortality was longer with amlodipine plus benazepril than with benazepril plus HCTZ, signifying better CV protection.[49]

A similar reduction in CV events occurred in patients with CAD receiving CCBs in addition to existing therapies. Among patients with CAD and normal BP in the CAMELOT study, the reduction in CV events was similar between amlodipine and enalapril (HR 0.81; 95% CI 0.63, 1.04; $p = 0.10$), and was significantly greater with amlodipine than with placebo (HR 0.69; 95% CI 0.54, 0.88; $p = 0.003$). There was no difference in CV events between the enalapril and placebo groups (HR 0.85; 95% CI 0.67, 1.07; $p = 0.16$).[57] In the ACTION study, nifedipine GITS plus best practice CV therapy was associated with significantly longer CV event- and procedure-free survival than with placebo plus best practice CV therapy (figure 2).[58] In addition, a subanalysis of the ACTION trial revealed that nifedipine GITS was associated with a significant reduction in the incidence of heart failure and the need for coronary angiography and bypass surgery. Among those with elevated BP at baseline, a 13% reduction in death and major CV events was observed.[61]

In INVEST, a similar incidence of the primary endpoint (all-cause death, nonfatal MI, or nonfatal stroke) was seen in patients with hypertension and CAD treated with a CCB or non-CCB strategy.[56] The study, which enrolled almost 14 000 patients, showed no significant difference between the two treatment arms for the primary endpoint (RR 0.98; 95% CI 0.90, 1.06).

These data suggest that CCBs can easily be combined with other antihypertensive classes, including ACE inhibitors and ARBs, in order to achieve BP control and CV risk reduction beyond that achieved with the respective monotherapies. Of note, there is a paucity of specific data available on CCBs, alone or in combination, for the treatment of hypertension or other CV disorders specifically in Latin America. However, recent registry data suggests that guideline-recommended treatment of hypertension in Latin America is improving. Baseline data from the REACH registry indicated that nearly 95% of Latin American patients either at risk of or with established CVD were treated with at least one antihypertensive agent. Similar to North America, β-blockers, ACE inhibitors, diuretics, and CCBs were most often prescribed.[62]

Despite the broad application of antihypertensive agents, the REACH registry data demonstrates that work is needed to bring patients to their BP goal, as >50% of Latin American patients were not at target BP levels.[62] Combination approaches were not described in these analyses, and direct morbidity and mortality outcomes due to poor BP control cannot be inferred; however, it is clear that optimal antihypertensive regimens require further evaluation in Latin American practice.

6. Additional Benefits of CCBs

As well as effects on BP control and CV risk reduction, CCBs have been associated with effects on a range of other aspects of the CV continuum. In patients with essential hyperten-

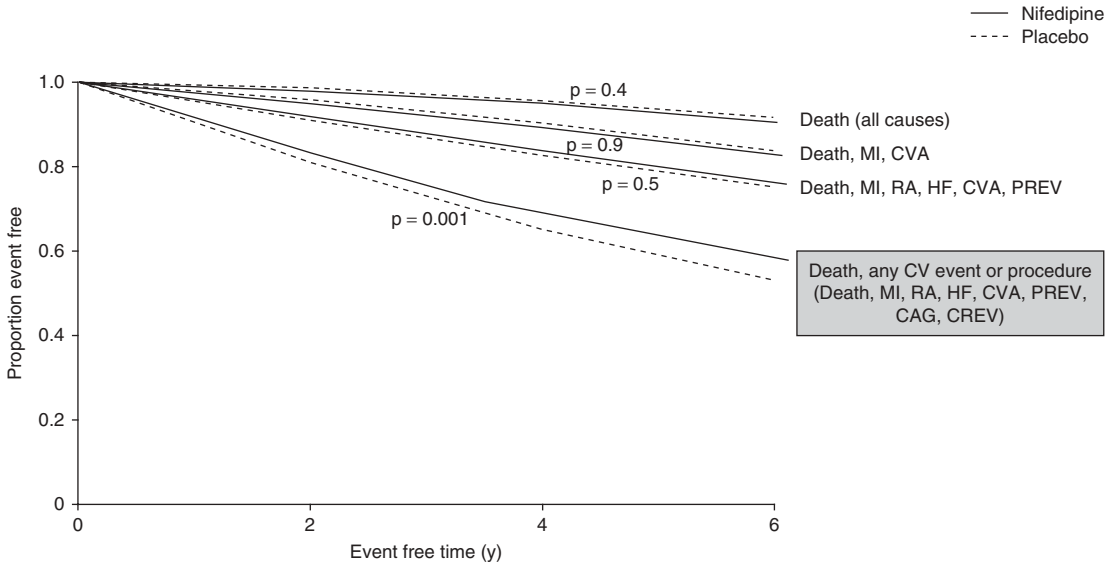

Fig. 2. Event-free survival with nifedipine or placebo in the ACTION study (reprinted with permission from *European Cardiovascular Disease*[60]). **CAG** = coronary angiography; **CREV** = coronary revascularization; **CV** = cardiovascular; **CVA** = cerebrovascular accident; **HF** = heart failure; **MI** = myocardial infarction; **PREV** = peripheral revascularization; **RA** = refractory angina.

sion, nifedipine monotherapy has been shown to improve endothelial function, oxidative stress, and antioxidative capacity.[63] These beneficial antioxidant effects of CCBs have also been seen with amlodipine[64] and verapamil.[65] Nifedipine has been shown to improve endothelial function in patients with familial hypercholesterolemia.[66] In the ENCORE study in patients with CAD, coronary endothelial function was improved to a greater extent with nifedipine than with either cerivastatin or placebo.[67] In the ENCORE II study, significant improvements in coronary endothelial function that persisted for at least 2 years, and a positive, non-significant trend in reduction of atheroma volume were observed with nifedipine.[33,68]

A non-significant trend towards a lower rate of mean intimal thickening with CCBs compared with diuretics was seen in two 3- or 4-year studies.[69,70] In VHAS, verapamil 240 mg once daily was compared with chlorthalidone 25 mg once daily.[70] Changes in intima-media thickness and between-group differences were small, but when analyzed by intima-media thickness strata, patients with plaques receiving verapamil had a significantly lower rate of CV events than chlorthalidone recipients.[70] In MIDAS, patients randomized to receive isradipine showed a trend towards a greater incidence of CV events compared with HCTZ recipients, but the between-group difference was not significant.[69]

CCBs have also demonstrated a positive effect on vasculature in patients with hypertension, CAD, or raised serum cholesterol levels.[71-76] Ancillary studies associated with the INSIGHT trial investigated the effects of nifedipine versus co-amilozide on carotid vascular wall changes and progression of coronary calcification in high-risk hypertensive patients.[71,74] Nifedipine was shown to have an effect on coronary calcification, significantly inhibiting the progression of coronary calcium deposition over a 3-year period, compared with co-amilozide, with a total calcium score of 39.9% versus a score of 77.8% in the co-amilozide group ($p = 0.02$).[74] In patients who completed the study investigating carotid wall changes, both groups had similar reductions in BP; however, intima-media thickness progression was seen in patients receiving co-amilozide (0.0077 mm/year) but not in the nifedipine group (–0.0007 mm/year; $p = 0.003$ vs co-amilozide) [figure 3].[71] Similarly, there were significant differences between the nifedipine and co-amilozide groups with respect to the changes in intima-media thickness (–0.004 vs +0.034 mm; $p = 0.002$) and cross-sectional area intima-media thickness (–0.332 vs +0.518 mm^2; $p = 0.005$).[71] Amlodipine also significantly reduced carotid intima-media thickness compared with placebo (–0.013 vs +0.033 mm; $p = 0.007$) in patients with CAD.[75] In another study of patients with CAD, nifedipine had no effect on existing atherosclerotic lesions, but significantly reduced the rate of formation of new lesions per patient by 28% compared with placebo (0.59 vs 0.82; $p = 0.034$).[73]

A meta-analysis of clinical trials that included data from 100 studies of eight dihydropyridine and four non-dihydropyridine CCBs showed no increase in serum lipid levels in patients receiving these agents.[77] The progression of atherosclerosis in symptomatic patients with elevated serum cholesterol levels

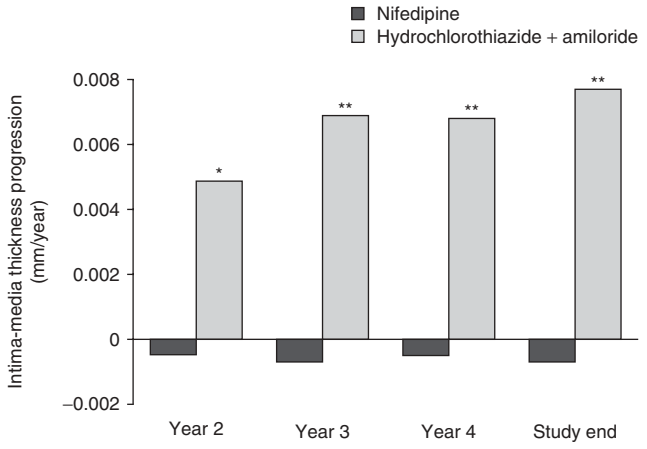

Fig. 3. Intima-media thickness progression rate with nifedipine and co-amilozide in the INSIGHT study. * $p < 0.01$, ** $p < 0.001$ vs zero within treatment group.[71]

was reduced in patients receiving CCBs plus pravastatin versus pravastatin alone, and in a cohort of Japanese patients with CAD receiving nifedipine versus ACE inhibitors.[72,76] In the Japanese study, nifedipine also reduced the number of new lesions compared with ACE-inhibitor treatment, although the difference was not significant ($p = 0.072$).[76] In the ACTION study, nifedipine was associated with a positive effect on coronary angiography, with the need for the procedure being reduced by 21% and 16% in normotensive and hypertensive patients, respectively; this was thought to be attributable to the anti-anginal, rather than BP-lowering, effects of this class of agents.[61]

CCBs have also been associated with beneficial effects on other systems. Analysis of the INSIGHT study results according to renal function showed that nifedipine may preserve renal function to a greater degree than diuretic-based treatments, with renal insufficiency occurring in significantly fewer patients receiving nifedipine than co-amilozide (2% vs 5%; $p < 0.01$).[78] In addition, both amlodipine and nifedipine have also been associated with a lower rate of new-onset diabetes than diuretics and β-blockers.[36,48] In the INSIGHT study, 4.3% of patients receiving nifedipine developed diabetes compared with 5.6% of patients in the co-amilozide group ($p = 0.02$),[36] while there was a 30% reduction in new-onset diabetes in patients receiving amlodipine compared with atenolol plus a thiazide in the ASCOT-BPLA study (HR 0.70; 95% CI 0.63, 0.78; $p < 0.0001$).[48] The lower incidence of new-onset diabetes seen in patients receiving CCBs in these studies may, in part, be a reflection of the increased incidence of new-onset diabetes experienced by individuals with hypertension treated with β-blockers and/or thiazide diuretics rather than protection invoked by CCBs *per se*.[79]

Long-term treatment with CCBs was effective at halting the progression of nephropathy in diabetic patients with hypertension and normoalbuminuria or microalbuminuria in a number of trials of between 36 weeks' and 3.6 years' duration (table II).[80,82-86] No significant increases from baseline in mean urinary albumin excretion were seen in any of the studies, and between 0% and 28% of individuals progressed from normo- to micro- or macroalbuminuria in these studies.[80,82-84,86] In one study, no significant difference in the incidence of persistent microalbuminuria was seen between patients receiving verapamil 240 mg/day or placebo.[80] No patients in any study receiving CCBs, or comparator agents, experienced a doubling of serum creatinine or onset of end-stage renal failure throughout active therapy.[82,84-86] A single study comparing CCBs with an ARB demonstrated a significant benefit for valsartan over amlodipine in diabetic patients with microalbuminuria over 24 weeks with similar reductions in BP.[81] CCBs compared with ACE inhibitors showed no between-treatment differences favoring a specific therapy.[80,82-86] A meta-analysis using data from four of these studies showed a significantly greater reduction in the risk of developing kidney disease (micro- or macroalbuminuria) with ACE inhibitors compared with CCBs (RR 0.58; 95% CI 0.40, 0.84).[87] However, no significant between-group difference in all-cause mortality was seen when data from six trials were analyzed (RR 0.84; 95% CI 0.26, 2.73).[87]

7. Tolerability of CCBs

CCBs have been shown to be well tolerated both as monotherapy and when combined with ACE inhibitors or ARBs. Adverse effects most commonly associated with CCBs include dizziness, headache, flushing, and peripheral edema.[35,36,48-50,53,57,58] Generally, adverse events are less prevalent with the long-acting CCB formulations; for example, the incidences of flushing, headache, dizziness, peripheral edema, and heart palpitations/tachycardia have been reported as being <5% in several studies of controlled-release nifedipine.[50,53,54,58] In addition, combination therapy with a CCB plus an ACE inhibitor has been shown to reduce the incidence of edema associated with CCB use.[88]

Several antihypertensive agents have been shown to induce adverse metabolic effects; for example, β-blockers increase triglycerides and decrease high-density lipoprotein (HDL)-cholesterol, and diuretics lower serum potassium levels and increase serum urea and uric acid levels.[34] In contrast, CCBs are generally metabolically neutral, with studies reporting no

effect of CCBs on serum levels of triglycerides, total cholesterol, low-density lipoprotein-cholesterol, or HDL-cholesterol.[72,76] Furthermore, as mentioned above, the risk of new diabetes is substantially lower than that observed with other antihypertensive classes.[36,48,89]

8. The Future of CCBs in the Treatment of Hypertension

CCBs are likely to remain a mainstay of treatment for hypertension in Latin America. Even as monotherapy, CCBs have demonstrated effective BP control (and, importantly, SBP control), with 70% of patients in the INSIGHT study achieving BP goal when receiving nifedipine.[36]

CCBs have also been shown to improve the CV risk profile to a greater degree than that expected by their BP-lowering effects alone and to provide additional advantages in terms of renal and vascular protection, reduction in new-onset diabetes cases, and lack of effect on metabolic parameters.

Given that the majority of patients on antihypertensives will eventually require multiple medications to control their BP, the place of CCBs in hypertension management will most likely be as part of combination therapy. Indeed, CCBs have been shown to be amenable to combination with other antihypertensive drugs, including ARBs and ACE inhibitors. The additive effect observed with combination therapy most likely occurs because of differing modes of action providing synergistic or complementary effects.

9. Conclusions

A main goal of antihypertensive treatment is to increase the length and quality of life in patients with this condition.[90] Several studies and meta-analyses have demonstrated that CCBs effectively reduce BP and CV morbidity and mortality, and display additional beneficial effects on vasculature and renal function. CCBs are also well tolerated and are amenable

Table II. Effect of calcium channel blockers (calcium channel antagonists) on proteinuria in adult patients with hypertension and type 2 diabetes mellitus[a]

Study (year)	Study design (duration)	Drug and dosage (mg/day)	No. of patients	Mean urinary albumin excretion (mg/day)		No. of patients reverting from normo- to micro- or macroalbuminuria
				baseline	endpoint	
BENEDICT study[80] (2004)	r, db, mc, pc (median 3.6 y)	Trandolapril 2	301	NR	NR	18/301*
		Verapamil 240	303	NR	NR	36/303
		Trandolapril/verapamil 2/180	300	NR	NR	17/300*
		Placebo	300	NR	NR	30/300
MARVAL study[81] (2001)	r, db, mc (24 wk)	Valsartan 80	169 microalbuminuric	83	49*	n/a
		Amlodipine 5	163 microalbuminuric	80	77	n/a
J-MIND study[82] (2001)	r, ol (24 mo)	Nifedipine 20–60	228	45	64	28/105
		Enalapril 5–20	208	42	74	15/95
Chan et al.[83] (2000)	r, db, pc (52 wk)	Enalapril 10	50	88	77†	4/18
		Nifedipine 40	52	82	97	7/25
FACET study[84] (1998)	r, ol (3.5 y)	Fosinopril 20	189	29	19	5/189
		Amlodipine 10	191	35‡	19	5/191
Scognamiglio et al.[85] (1997)	r, db (36 wk)	Captopril 50–100	38	23	27	NR
		Nitrendipine 20–40	37	12	13	NR
Velussi et al.[86] (1996)	r, db (3 y)	Cilazapril 2.5	13 normoalbuminuric	13	9	0/13
		Amlodipine 5	13 normoalbuminuric	12	9	0/13
		Cilazapril 2.5	9 microalbuminuric	71	52†	n/a
		Amlodipine 5	9 microalbuminuric	56	39†	n/a

a Supplementary data obtained from Strippoli et al.[87] (2005).

db = double-blind; **mo** = months; **mc** = multicenter; **n/a** = not applicable; **NR** = not reported; **ol** = open-label; **pc** = placebo-controlled; **r** = randomized. * $p < 0.01$ vs placebo; † $p < 0.01$ vs baseline; ‡ $p < 0.05$ vs fosinopril.

to combination therapy with either ARBs or ACE inhibitors. Therefore, these agents represent an appropriate choice of antihypertensive agent in Latin America, where hypertension and CV risk remain substantial health issues.

Acknowledgments

Medical writing assistance was provided by Claire Byrne and Sheridan Henness, PhD, of *in*Science Communications, a part of the Wolters Kluwer organization, with funding from Bayer Schering.

This document is the result of a preparatory work done by the following invited experts from different countries in Latin America during a reunion held in New Orleans in December 2008:

Latin American Expert Group on Cardiovascular and Metabolic Risk: Luis Alcocer, MD, MPH; Mario Bendersky, MD, PhD; Julio Acosta, MD; Miguel Urina-Triana, MD, FACC; Hugo Hérnández, MD; Oscar Sada, MD; Alberto Rubio, MD; Pablo Rodríguez, MD; Alberto Cafferata, MD; Andréia Loures-Vale, MD; Celso Amodeo, MD; Mauricio Varela Ramos, MD; Franklin Haase, MD; Bolivar Tejada, MD; Roberto Lecaro, MD; Carlos Galán, MD; Roberto López, MD; Marco Antonio Lavagnino, MD (Bayer Schering Pharma Staff); and Guido Senatore, MD (Bayer Schering Pharma Staff).

Dr Alcocer serves as a consultant and has received fees from speaking engagements from Abbott Laboratories, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Merck, Novartis, Pfizer, Roche, sanofi-aventis, and Servier. Dr Urina-Triana has received grants from Bayer, Bristol-Myers Squibb, Frosst Laboratories, Novartis, Pfizer, and sanofi-aventis. Dr Bendersky and Dr Acosta have no conflicts of interest that are directly relevant to the content of this review.

References

1. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. Am Heart J 1991 Apr; 121 (4 Pt 1): 1244-63
2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003 May 21; 289 (19): 2560-72
3. Lanas F, Avezum A, Bautista LE, et al. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. Circulation 2007 Mar 6; 115 (9): 1067-74
4. Piegas LS, Avezum A, Pereira JC, et al. Risk factors for myocardial infarction in Brazil. Am Heart J 2003 Aug; 146 (2): 331-8
5. Ciruzzi M, Schargrodsky H, Pramparo P, et al. Attributable risks for acute myocardial infarction in four countries of Latin America. Medicina (B Aires) 2003; 63 (6): 697-703
6. Touboul PJ, Hernandez-Hernandez R, Kucukoglu S, et al. Carotid artery intima media thickness, plaque and Framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA study. Int J Cardiovasc Imaging 2007 Oct; 23 (5): 557-67
7. Sanchez RA, Ayala M, Baglivo H, et al. Latin American guidelines on hypertension. J Hypertens 2009 May; 27 (5): 905-22
8. Lip GY, Makin AJ. Treatment of hypertension in peripheral arterial disease. Cochrane Database Syst Rev 2003; (4): CD003075
9. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics – 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009 Jan 27; 119 (3): e21-181
10. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002 Dec 14; 360 (9349): 1903-13
11. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003 Nov; 21 (11): 1983-92
12. Ostchega Y, Yoon SS, Hughes J, et al. Hypertension awareness, treatment and control: continued disparities in adults. United States, 2005-2006. Hyattsville (MD): National Center for Health Statistics, NCHS Data Brief No. 3, 2008
13. Yach D, Hawkes C, Gould CL, et al. The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA 2004 Jun 2; 291 (21): 2616-22
14. American Heart Association. International cardiovascular disease statistics: 2002 [online]. Available from URL: http://www.americanheart.org/downloadable/heart/1023898043312CVD_stats.pdf [Accessed 2009 Jan 19]
15. Cubillos-Garzon LA, Casas JP, Morillo CA, et al. Congestive heart failure in Latin America: the next epidemic. Am Heart J 2004 Mar; 147 (3): 412-7
16. Royer M, Castelo-Branco C, Blumel JE, et al. The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III): prevalence of the metabolic syndrome in postmenopausal Latin American women. Climacteric 2007 Apr; 10 (2): 164-70
17. Bustos P, da Silva AA, Amigo H, et al. Metabolic syndrome in young adults from two socioeconomic Latin American settings. Nutr Metab Cardiovasc Dis 2007 Oct; 17 (8): 581-9
18. James WP. The epidemiology of obesity: the size of the problem. J Intern Med 2008 Apr; 263 (4): 336-52
19. Hernandez-Hernandez R, Armas-Padilla MC, Armas-Hernandez MJ, et al. Hypertension and cardiovascular health in Venezuela and Latin American countries. J Hum Hypertens 2000 Apr; 14 Suppl. 1: S2-5
20. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995 Mar; 25 (3): 305-13
21. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet 2008 May 3; 371 (9623): 1513-8
22. Abegunde DO, Mathers CD, Adam T, et al. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007 Dec 8; 370 (9603): 1929-38
23. Ordunez P, Silva LC, Rodriguez MP, et al. Prevalence estimates for hypertension in Latin America and the Caribbean: are they useful for surveillance? Rev Panam Salud Publica 2001 Oct; 10 (4): 226-31
24. Schargrodsky H, Hernandez-Hernandez R, Champagne BM, et al. CARMELA: assessment of cardiovascular risk in seven Latin American cities. Am J Med 2008 Jan; 121 (1): 58-65
25. Nigro D, Vergottini JC, Kuschnir E, et al. Epidemiología de la hipertensión arterial en la ciudad de Córdoba. Argentina Rev Fed Arg Cardiol 1999; 28: 1969-75
26. Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens 2007 Sep; 25 (9): 1751-62
27. Consenso de Hipertensión Arterial. Consejo Argentino de Hipertensión Arterial. Rev Arg Cardiol 2007; 75 Suppl. 3: 1-43
28. Ribeiro AB, Zanella MT, Kohlmann Jr O. Guidelines for treatment of hypertension in Latin America: the Brazilian experience. Clin Exp Hypertens 1999 Jul-Aug; 21 (5-6): 683-92

29. Burlando G, Sanchez RA, Ramos FH, et al. Latin American consensus on diabetes mellitus and hypertension. J Hypertens 2004 Dec; 22 (12): 2229-41
30. Fuentes R, Ilmaniemi N, Laurikainen E, et al. Hypertension in developing economies: a review of population-based studies carried out from 1980 to 1998. J Hypertens 2000 May; 18 (5): 521-9
31. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997 May 17; 349 (9063): 1436-42
32. Arredondo A, Zuniga A. Epidemiologic changes and economic burden of hypertension in Latin America: evidence from Mexico. Am J Hypertens 2006 Jun; 19 (6): 553-9
33. Rubinstein A, Alcocer L, Chagas A. High blood pressure in Latin America: a call to action. Ther Adv Cardiovasc Dis 2009; 3 (4): 259-85
34. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. Am J Hypertens 2001 Mar; 14 (3): 241-7
35. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004 Jun 19; 363 (9426): 2022-31
36. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000 Jul 29; 356 (9227): 366-72
37. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000 Jul 29; 356 (9227): 359-65
38. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003 Apr 23-30; 289 (16): 2073-82
39. Dubois C, Blanchard D. Efficacy and safety of nicardipine in 29,104 patients with hypertension. Clin Ther 1989 Jul-Aug; 11 (4): 452-60
40. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998 Jun 13; 351 (9118): 1755-62
41. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997 Sep 13; 350 (9080): 757-64
42. Pastor-Barriuso R, Banegas JR, Damian J, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med 2003 Nov 4; 139 (9): 731-9
43. Lawes CM, Vander Hoorn S, Law MR, et al. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. J Hypertens 2006 Mar; 24 (3): 423-30
44. Mancia G, Ruilope L, Palmer C, et al. Effects of nifedipine GITS and diuretics in isolated systolic hypertension: a subanalysis of the INSIGHT study. Blood Press 2004; 13 (5): 310-5
45. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000 Dec 9; 356 (9246): 1955-64
46. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002 Dec 18; 288 (23): 2981-97
47. Mancia G, Brown M, Castaigne A, et al. Outcomes with nifedipine GITS or coamilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension 2003 Mar; 41 (3): 431-6
48. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005 Sep 10-16; 366 (9489): 895-906
49. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008 Dec 4; 359 (23): 2417-28
50. Kuschnir E, Bendersky M, Resk J, et al. Effects of the combination of low-dose nifedipine GITS 20 mg and losartan 50 mg in patients with mild to moderate hypertension. J Cardiovasc Pharmacol 2004 Feb; 43 (2): 300-5
51. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther 2008 Apr; 30 (4): 587-604
52. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther 2007 Apr; 29 (4): 563-80
53. Hasebe N, Kikuchi K. Controlled-release nifedipine and candesartan low-dose combination therapy in patients with essential hypertension: the NICE-Combi (Nifedipine and Candesartan Combination) study. J Hypertens 2005 Feb; 23 (2): 445-53
54. Saito I, Saruta T. Controlled release nifedipine and valsartan combination therapy in patients with essential hypertension: the Adalat CR and Valsartan Cost-Effectiveness Combination (ADVANCE-Combi) study. Hypertens Res 2006 Oct; 29 (10): 789-96
55. Frishman WH, Hainer JW, Sugg J. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). Am J Hypertens 2006 Apr; 19 (4): 388-95
56. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril Study (INVEST) – a randomized controlled trial. JAMA 2003 Dec 3; 290 (21): 2805-16
57. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study – a randomized controlled trial. JAMA 2004 Nov 10; 292 (18): 2217-25
58. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 2004 Sep 4-10; 364 (9437): 849-57
59. Mancia G. The TALENT study. Eur Cardiol Extract Touch Brief 2008; 4 (1): 75-8
60. Messerli FH, Noll G, Lindholm LH, et al. The role of dihydropyridine calcium channel blockers in the treatment of hypertension and cardiovascular disease-an update. Eur Cardiovasc Dis 2006: 16-20
61. Lubsen J, Wagener G, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial. J Hypertens 2005 Mar; 23 (3): 641-8
62. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006 Jan 11; 295 (2): 180-9

63. Taddei S, Virdis A, Ghiadoni L, et al. Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. Hypertension 2001 Mar; 37 (3): 943-8

64. Ghiadoni L, Magagna A, Versari D, et al. Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension 2003 Jun; 41 (6): 1281-6

65. Noronha-Dutra AA, Steen-Dutra EM, Woolf N. An antioxidant role for calcium antagonists in the prevention of adrenaline mediated myocardial and endothelial damage. Br Heart J 1991 Jun; 65 (6): 322-5

66. Verhaar MC, Honing ML, van Dam T, et al. Nifedipine improves endothelial function in hypercholesterolemia, independently of an effect on blood pressure or plasma lipids. Cardiovasc Res 1999 Jun; 42 (3): 752-60

67. The ENCORE I Study (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function). Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease. Circulation 2003 Jan 28; 107 (3): 422-8

68. Luscher TF, Pieper M, Tendera M, et al. A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. Eur Heart J 2009 Jul; 30 (13): 1590-7

69. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. JAMA 1996 Sep 11; 276 (10): 785-91

70. Zanchetti A, Rosei EA, Dal Palu C, et al. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. J Hypertens 1998 Nov; 16 (11): 1667-76

71. Simon A, Gariepy J, Moyse D, et al. Differential effects of nifedipine and coamilozide on the progression of early carotid wall changes. Circulation 2001 Jun 19; 103 (24): 2949-54

72. Jukema JW, Zwinderman AH, van Boven AJ, et al. Evidence for a synergistic effect of calcium channel blockers with lipid-lowering therapy in retarding progression of coronary atherosclerosis in symptomatic patients with normal to moderately raised cholesterol levels. The REGRESS Study Group. Arterioscler Thromb Vasc Biol 1996 Mar; 16 (3): 425-30

73. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of angiographic progression of coronary artery disease by nifedipine: results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). INTACT Group Investigators. Lancet 1990 May 12; 335 (8698): 1109-13

74. Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. Hypertension 2001 Jun; 37 (6): 1410-3

75. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation 2000 Sep 26; 102 (13): 1503-10

76. Shinoda E, Yui Y, Kodama K, et al. Quantitative coronary angiogram analysis: nifedipine retard versus angiotensin-converting enzyme inhibitors (JMIC-B side arm study). Hypertension 2005 Jun; 45 (6): 1153-8

77. Kasiske BL, Ma JZ, Kalil RS, et al. Effects of antihypertensive therapy on serum lipids. Ann Intern Med 1995 Jan 15; 122 (2): 133-41

78. de Leeuw PW, Ruilope LM, Palmer CR, et al. Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial. Arch Intern Med 2004 Dec 13-27; 164 (22): 2459-64

79. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 2000 Mar 30; 342 (13): 905-12

80. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004 Nov 4; 351 (19): 1941-51

81. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 2002 Aug 6; 106 (6): 672-8

82. Baba S. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. Diabetes Res Clin Pract 2001 Dec; 54 (3): 191-201

83. Chan JC, Ko GT, Leung DH, et al. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. Kidney Int 2000 Feb; 57 (2): 590-600

84. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998 Apr; 21 (4): 597-603

85. Scognamiglio R, Nosadini R, Marin M, et al. Evaluation of the efficacy and tolerability of nitrendipine in reducing both pressure and left ventricular mass in hypertensive type 2 diabetic patients. Diabetes Care 1997 Aug; 20 (8): 1290-2

86. Velussi M, Brocco E, Frigato F, et al. Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. Diabetes 1996 Feb; 45 (2): 216-22

87. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev 2005; (4): CD004136

88. Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol 2000 Dec 1; 86 (11): 1182-7

89. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007 Jan 20; 369 (9557): 201-7

90. Alcocer L, Parra JZ, Hernández HH. Una versión minimalista sobre el tratamiento de la hipertensión arterial: esquemas de tratamiento antihipertensor. Rev Mex Cardiol 2008; 19: 3-6

Correspondence: Dr *Luis Alcocer*, Universidad Nacional Autónoma de México, Chief, Cardiology Services, Hospital General de México, Circuito Fuentes del Pedregal 789, Tlalpan D.F., México 14140.
E-mail: hospitalgeneral@hotmail.com